Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 9-16 and 21 are pending in the application. Claim 15 has been amended in order to more clearly define the subject matter of the claimed invention. The title has been amended according to the Examiner's suggestions. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Answer to Traversal

The Examiner has asserted that Applicants are required to remove the recitation of "non-human animal" from claim 15 because allegedly, the "scope and issues regarding subject matter involving transgenic animals are in conflict with examination of the remainder of the claimed invention." (Paper No. 14, page 2.) The Examiner's comments are in response to Applicants' Reply to Restriction Requirement and Amendment and Reply Under 37 C.F.R. § 1.111 ("Reply"), dated January 29, 2002. In the Reply, Applicants argued that restriction between Group I and Group II was improper because examination of the subject matter of Groups I and II together would not entail a serious burden on the Examiner. Applicants explained (and the Examiner appears to agree in the instant Office Action) that if the nucleic acid of claim 9 is found to be novel and unobvious, then a mammalian cell

comprising the nucleic acid of claim 9 would also be novel and unobvious because claim 9 is not limited by the presence of the nucleic acid in a particular cell type. The Examiner, however, has acknowledged that he may have confused the issue by indicating in his previous Office Action that claim 15 recited "non-human animal *cell*" although the claim, in fact, recites "non-human animal."

Applicants assert that in either instance, Applicants' arguments in the Reply are applicable. That is, whether or not claim 15 recites "non-human animal" or "non-human animal cell," it will be found novel and unobvious if claim 9 is found novel and unobvious. Thus, a search of the subject matter of claims 9 and 15 would not entail a serious burden on the Examiner. Nonetheless, the Examiner, has stated that the "scope and issues regarding subject matter involving transgenic animals are in conflict with examination of the remainder of the claimed invention." Applicants disagree with this statement. The Examiner has failed to explain how the issue regarding the subject matter involving transgenic animals is in conflict with examination of the remainder of the claimed invention. Further, the existence or absence of a "conflict" is not the proper standard to be utilized in maintaining a restriction requirement. The appropriate standard is whether it would entail a "serious burden" for the Examiner to examine both groups. As discussed above, Applicants submit that it would not entail a serious burden for the Examiner to examine both groups of claims.

However, in the interest of advancing prosecution and without acquiescence in the Examiner's assertions, Applicants have amended claim 15 to remove the subject matter which the Examiner has alleged causes a "conflict" with examination of the remained of the

claimed invention. Accordingly, Applicants respectfully request that any rejection and/or objection to claim 15 be withdrawn. Applicants remind the Examiner that the previous election of Group I has not been withdrawn and that the election of Group I is with traverse.

II. Claim Objections

In the section of the Office Action entitled "Claim Objections," the Examiner has objected to the title of the claimed invention. (Paper No. 14, page 2.) Applicants respectfully traverse this rejection. Solely to advance prosecution and without acquiescence in the Examiner's objection, Applicants have amended the title pursuant to the Examiner's previous suggestions. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the objection.

The Examiner has also objected to claim 15 because it recites "non-human animal." (Paper No. 14, page 2.) In the amendments above, Applicants have amended claim 15 so as to render the Examiner's objection moot. As discussed in Part I of these Remarks, Applicants disagree with the Examiner's basis for the objection and have amended the claim solely to advance prosecution.

III. Claims Rejections Under 35 U.S.C. § 103

The Examiner has maintained the rejection of claims 9-16 under 35 U.S.C. § 103 as allegedly unpatentable in view of Lee *et al.* in view of Kordula *et al.* (Paper No. 14, page 3.) The Examiner has stated that:

> [B]ased on the need for a better expression vector and large-scale purification for the protein of Kordula *et al.*, one of ordinary skill in the art would have been motivated to substitute the cDNA of Kordula *et al.*, which has the 3'-UTR

> deleted, for the nucleic acid encoding the sialytransferase in the vector of Lee *et al.*, for the purpose of producing purified protein on a large-scale, which cannot necessarily be accomplished using the vector and expression system of Kordula *et al.*

(*Id.*) Applicants respectfully disagree and traverse the rejection.

Kordula *et al.* is concerned with the expression of horse elastase inhibitor (HLEI) in a prokaryotic expression system. Lee *et al.* is concerned with the expression of sialytransferase in a mammalian system, the sialytransferase gene having a mammalian signal peptide attached thereto which causes the resulting protein to be secreted from the cell.

In the present invention, it was completely unexpected that the 3'-UTR acts to direct mRNAs encoding intracellular proteins to intracellular locations and away from the endoplasmic reticulum. Therefore, in order to obtain secretion of an intracellular protein, not only must a nucleic acid encoding a signal peptide be attached to the mRNA encoding the intracellular protein (as is well known), but the native 3'-UTR of the mRNA must also be disrupted to prevent it from competing with the signal peptide.

The Examiner is combining a document which discloses a nucleic acid encoding an intracellular mammalian protein with a document which discloses a eukaryotic expression vector with a nucleic acid encoding a signal peptide as the basis of the rejection. However, there is nothing in these documents which provides one of ordinary skill in the art the motivation to disrupt the native 3'-UTR to obtain improved secretion of an intracellular protein (i.e., a protein which is not normally secreted from a cell). If no such motivation is present, then one of ordinary skill in the art cannot obtain the claimed invention.

The Examiner contends that the motivation to combine Kordula *et al.* (which relates only to expression in prokaryotes) with Lee *et al.* (which relates only to expression in eukaryotes) is to be found in the desire to have "large scale purification, [of HLEI] and may require a more efficient expression vector than pKK233-2."

There is nothing in this statement that suggests that anything other than a more efficient *prokaryotic* expression system is needed. Thus, there is no motivation for one of ordinary skill in the art to use a eukaryotic system. Indeed, the fact that a prokaryotic system (plasmid pKK233-2) had been shown successfully to produce recombinant HLEI ("Expression of HLEI cDNA in E. coli led to the accumulation of large amounts of protein in both the cytoplasm and in the inclusion bodies") which is active would point one of ordinary skill in the art to using an improved prokaryotic system, because of the ease of use of such systems compared to the known expense and difficulty in using a eukaryotic system. The Examiner surely cannot suggest that one of ordinary skill in the art, knowing that a protein could be successfully produced in a prokaryotic system, but looking to improve the efficiency of expression, would look to a mammalian system rather than an alternative prokaryotic system.

There must be a teaching or suggestion within the prior art, or within the general knowledge of a person of ordinary skill in the art of the invention, to look to particular sources of information, to select particular elements, and to combine them in the way they were combined by the inventor. *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534 (Fed. Cir. 1998). "A general incentive does not make a particular result obvious, nor does the existence of

techniques by which those efforts can be carried out." *In re Deuel*, 34 USQP2d 1210, 1216 (Fed. Cir. 1995). However, the Examiner has failed to identify any *particular* motivation in Kordula *et al.* to use the expression vector taught in Lee *et al.*

Even assuming, *arguendo,* that one of ordinary skill in the art would be motivated to increase the production of HLEI as discussed in Kordula *et al.*, he or she would not have a reasonable expectation of success in choosing the expression system of Lee *et al.* This is because the 3'-UTR of HLEI is absent in Kordula *et al.* The reason why the 3'-UTR of HLEI is not present in Kordula *et al.* is because bacterial mRNAs do not have 3'-UTRs. Before the present invention (and the teachings provided in the specification), one of ordinary skill in the art would believe that, for expression in mammalian cells, the 3'-UTR of a gene would be needed. Therefore, if one of ordinary skill in the art was motivated to make the combination the Examiner is suggesting, he or she would ensure that the HLEI gene had its 3'-UTR to ensure a reasonable expectation of correct secretion from the mammalian cells of Lee *et al.* To insist that one of ordinary skill in the art would remove or otherwise disrupt the 3'-UTR of HLEI is to use the teachings of Applicants' specification in a hindsight manner to form the basis of an obviousness rejection. This is improper. Further, Applicants note that Lee *et al.* represents one of the first reports, if not the first report, of secretion of an intracellular protein from mammalian cells. The novelty of the method could not have provided one of ordinary skill in the art with a reasonable expectation of success.

Applicants assert that one of ordinary skill in the art would not have a motivation to combine the cited references. A general incentive to improve upon the prokaryotic expression system taught in Kordula *et al.* would not lead one to the particular eukaryotic

system taught in Lee *et al*. Even assuming, *arguendo*, that one of ordinary skill in the art would find a motivation to combine, he or she would not reasonably expect the combination to successfully lead to the claimed invention. As discussed, absent Applicants' teachings, one of ordinary skill in the art would not have expected that a deletion or other disruption of the 3'-UTR of mRNA encoding a protein would lead to secretion of the encoded protein in mammalian cells. In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the invention.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Date: August 8, 2002

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Version with markings to show changes made

The application has been amended as follows:

In the Title:

At page 1, line 1:

Expression system for the secretion of intracellular proteins [Nucleic Acid Constructs Involved in the Regulation of Protein Secretion]

In the Claims:

15. (Once amended) A mammalian cell comprising the nucleic acid molecule of claim 9 [, wherein said cell is in a cell culture or in a non-human animal].